REMARKS

Claims 3, 4, 7, 8, 18, 31 and 33-37 are pending in this application. Of these, claims 33-37 are withdrawn. Applicants have amended claim 18 hereinabove but have not canceled or added any claim. Accordingly, claims 3, 4, 7, 8, 18 (as amended), and 31 are pending and under examination.

Previous Rejections Under 35 U.S.C. §112

As an initial matter applicants note that all rejections under 35 U.S.C. §112 have been withdrawn.

Information Disclosure Statement; Copending Applications

In the January 23, 2008 Office Action, the Examiner indicated that the listing of references in the specification is not a proper information disclosure statement, and that unless the references have been cited by the Examiner on form PTO-892, these references have not been considered. The Examiner further indicated that applicants must bring to the attention of the Examiner copending applications which are material to patentability of the subject application.

In response, applicants note that an Information Disclosure Statement in accordance with 37 C.F.R. 1.97 and 1.98 with substitute form PTO-1449 listing all references, including related patents and copending patent applications was submitted with a September 17, 2007 Amendment. In addition, a Supplemental Information Disclosure Statement was submitted on January 22, 2008. Applicants further note that with the January 23, 2008 Office Action, the Examiner included initialed copies of the substitute form PTO-1449 submitted with the September 17, 2007 Information Disclosure Statement. Applicants respectfully request that the Examiner consider the listed references submitted with the January 22, 2008 Supplemental

Information Disclosure Statement, a copy of which is attached hereto as **Exhibit A**, and initial and return a copy of the substitute form PTO-1449 submitted herewith.

Obviousness-Type Double Patenting Rejection

The Examiner maintained the rejection of claims 3, 4, 7, 8, 18 and 31 on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-6 of U.S. Patent No. 6,831,073.

In response, applicants respectfully traverse the Examiner's ground of rejection.

Applicants maintain that the present invention is based on the unexpected discovery that a lower progestative dose may be used to induce enometrium atrophy with good control of bleeding. Applicants' claimed invention, specifically the recited 0.625 to 1.25 mg range of nomegestrol acetate per daily dose, is unobvious over claims 1-6 of U.S. Patent No. 6,831,073 because the claimed dose yields an unexpected result, namely, the surprising decoupling of the anti-estrogenic effect of nomegestrol acetate from its progestational effect when it is administered in continuous combination with estrogens. As indicated on page 22 of the instant specification, the highest percentage of atrophic endometria was found at the lowest progestative dose. These results are unexpected; because one skilled in the art would have expected low doses which are insufficient to induce secretory transformation of the endometrium would also be insufficient to preventing growth of the uterine mucose and keep it in an atrophic condition.

Moreover, claims 1-6 of U.S. 6,831,073 provides methods for treating estrogenic deficiencies in post menopausal women, while applicants' claimed invention provides for method of treating a menopausal

woman.

In view of the preceeding remarks, applicants maintain that amended claim 18 and 31 and claims dependent thereon are unobvious over claims 1-6 of U.S. Patent No. 6,831,073, and respectfully request that the Examiner reconsider and withdraw the rejection based on nonstatutory obviousness-type double patenting.

Rejections Under 35 U.S.C. §103(a)

1.Jamin in view of Martindale, Bazin et al., Paris et al. and Hodgen

The Examiner rejected claims 3, 4, 7, 8, 18 and 31 under 35 U.S.C. 103(a) as allegedly unpatentable over Jamin, Rev.fr.Gyncol.Obstet (1992), Vol. 87, No. 6, pp 370-376 in view of Martindale (1993), Bazin et al., Paris et al., and Hodgen (U.S. Pat. 5,552,294). Specifically, the Examiner asserted that the prior art discloses the combination of estrogens and progestogens in oral contraceptives, such as tablets, and that the equivalent dosages and dosage forms for estrogens and progestogens are known. The Examiner also asserted that the prior art discloses doses of nomegestrol acetate of 2.5 mg-5mg/day, estradiol or estradiol valerate at 1-2 mg/day or equine conjugated estrogen at 0.3 to 1.25 mg daily and transdermal estradiol at doses of 50 mg and up to 100 mg. The Examiner further asserted that the prior art discloses administration of estrogens and progestogens in cycles of 20, 21, 22, 23-25 days per 28 days and that nomegestrol acetate at said dosage levels results in very low levels of estradiol. In addition, the Examiner asserted that the prior art discloses the combination of 5 mg/day of nomegestrol acetate and 50 mg/day transdermal estradiol in cycle of 20 days/28 days for contraception which avoids the problems caused by progestogen only formulations. Based on the foregoing, the Examiner alleged that one of ordinary skill in the art would have been motivated to combine nomegestrol acetate at a dosage of 2.5mg-5 mg/day with oral estradiol, ester thereof, such as valerate (1-2

mg/day) or equine conjugated estrogen (0.3 to 1.25 mg/day) with the expectation that the oral form of estradiol or equine conjugated estrogen at said dosages would be comparable to the transdermal estradiol in avoiding the problems of low estradiol levels due to the administration of nomegestrol acetate and that a cycle of 20, 21, 22, 23-25 days/28 days would be effective in blocking pregnancies. The Examiner further indicated that since the amounts and days disclosed in the prior art fall within, overlap or near that claimed, the ranges and amounts claimed are prima facie obvious in view of the prior art.

In response, applicants respectfully traverse the Examiner's ground of rejection.

Applicants' invention provide (1) a method of treating a menopausal woman comprising continuously orally administering without interruption to such menopausal woman a composition containing from 0.5 to 1.5 mg of free estradiol or 1.5 to 2 mg of an estradiol ester, and from 0.625 to 1.25 mg of nomegestrol acetate per daily dose and (2) a pharmacetucal composition in oral administrable form comprising, in combination, from 0.5 to 1.5 mg of free estradiol or 1.5 to 2 mg of an esterified estradiol and from 0.625 to 1.25 mg of nomegestrol acetate.

Applicants maintain that Jamin in combination with Martindale, Bazin et al., Paris et al., and Hodgen do not render obvious the claimed methods or compositions.

Applicants maintain that the present invention is based on the unexpected discovery that a lower progestative dose may be used to induce endometrium atrophy with good control of bleeding. Applicants maintain that the 0.625 to 1.25 mg range of nomegestrol acetate per daily dose recited in claims 18 and 31 is not disclosed in any cited reference, and therefore no combination of the cited

references can render applicants' claimed invention obvious. Applicants further maintain that based on the teaching of the prior art, one skilled in the art would not have used such a low dose of nomegestrol acetate per daily dose in the claimed invention. In fact, the Examiner herself acknowledges based on the cited references that "one of ordinary skill in the art would have been motivated to combine nomegestrol acetate at a dosage of 2.5 mg-5 mg/day with oral estradiol." This is not applicants' claimed range. Applicants maintain that the claimed low dose of nomegestrol acetate provided an unexpected result. One skilled in the art would not have expected that such a low dose would result in the surprising and unpredictable result of decoupling the anti-estrogenic effect of nomegestrol actetate from its progestational effect when administered in combination with estrogens. In addition, and as indicated on page 22 of the instant specification, the highest percentage of atrophic endometria was found at the lowest progestative dose. These results are unexpected and were unpredictable because one skilled in the art would have expected that low doses which are insufficient to induce secretory transformation of the endometrium would also be insufficient to preventing growth of the uterine mucose and keep it in an atrophic condition.

On page 12 of the January 23, 2008 Office Action, the Examiner stated that "[t]he consideration that the amount of estradiol in Jamin would not contribute to the contraceptive effect, however, applicants provide no evidence of the same. Further the prior art discloses that suprresion of LH and FSH peaks is a function of both estrogen and progestrogen components of a combined oral contraceptive. As such, potentiation of the antiovulatory activity of nomegestrol by estradiol or its derivative is not unexpected and the declaration of inventor Thomas does not appear to show unexpected activity."

Applicants respectfully disagree. In the Declaration of Jean-Louis Thomas submitted on February 2, 2006, a copy of which is attached hereto as **Exhibit B**, Dr. Thomas declared that low doses of nomegestrol acetate in combination with an estradiol protect the endometrium because the endometrium remains atrophic. Such low doses do not induce a secretory transformation of the endometrium and keep the endometrium protected in an atrophic phase. This is surprising and unexpected. It would not have been obvious to one skilled in the art that the higher doses of nomegestrol taught in the prior art could be replaced with the doses claimed in the subject application.

2. Plunkett et al. in view of Blanc et al.

The Examiner maintained the rejection of claims 3, 4, 7, 8, 18 and 31 under 35 U.S.C. §103(a) as allegedly obvious over Plunkett et al. in view of Blanc et al. Specifically, the Examiner asserted that Plunkett et al. teach a method of hormonal treatment for menopausal disorders involving continuous administration of progestagens and estrogens. The Examiner further asserted that Blanc et al. teach continuous hormone replacement therapy by combining nomegesterol acetate and gel, patch, or oral estrogen.

In response, applicants respectfully traverse the Examiner's ground of rejection.

As stated above, applicants' invention provides in claim 18 a method of treating a menopausal woman comprising continuously orally administering without interruption to such menopausal woman a composition containing from 0.5 to 1.5 mg of free estradiol or 1.5 to 2 mg of an estradiol ester, and from 0.625 to 1.25 mg of nomegestrol acetate per daily dose. Claim 31 recites a pharmaceutical composition in oral administrable form comprising, in combination, from 0.5 to 1.5 mg of free estradiol or 1.5 to 2 mg of an esterified estradiol and from 0.625 to 1.25 mg of nomegestrol

acetate.

Applicants maintain that Plunkett et al. in combination with Blanc et al. do not render obvious either the claimed method or the claimed composition.

Applicants maintain that Plunkett et al. do not disclose nomegestrol acetate as a progestin candidate for use in hormonal therapy. Applicants further maintain that although Plunkett et al. specify certain ranges of dosage for certain progestins in Table IB, Plunkett et al. do not disclose which progestins are to be used or which dose is to be used with each type of progestins. In addition, of the progestatives disclosed, namely levonorgestrel, norethisterone, norethisterone acetate, norgestrel, ethynodiol diacetate, dihydrogesterone, MPA, norethylnodrel, allylestrenol, lynoestrenol, quingestanol acetate, medrogestone, norgestrienone, ethisterone and cyproterone, none are disclosed in the dosage range recited in claims 18 and 31. Specifically, none of these progestatives are administered in a dose from 0.625 to 1.25 mg. Therefore, no combination of the cited references can render obvious applicants' claimed invention.

Applicants maintain that Blanc et al. also fail to disclose the dosage of applicants' claimed invention. Blanc at al. teach that nomegestrol acetate may be used in combination with estrogen at a dose of 2.5 mg/day. As discussed above, the present invention is based on the unexpected discovery that a lower progestative dose may be used to induce endometrium atrophy with good control of bleeding. Specifically, the recited low dose of 0.625 to 1.25 mg nomegestrol acetate per day is novel and is unobvious because it yields an unexpected and unpredictable result relative to the teaching of the cited reference in view of Blanc et al. Applicants maintain that the decoupling of the anti-estrogenic effect of nomegestrol acetate from its progestational effect when it is administered in continuous

combination with estrogens is surprising, unexpected, and unpredictable in view of the cited prior art. One skilled in the art would not have expected such low doses of nomegestrol acetate to induce endometrium atrophy. Accordingly, applicants maintain that the combination of Plunkett et al. and Blanc et al. does not render the claimed invention obvious.

In view of these remarks, applicants maintain that claims 3, 4, 7, 8, 18 and 31, recite unobvious subject matter over the asserted combinations of the cited prior art and request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §103(a).

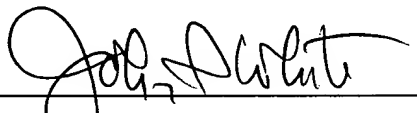
Conclusion

For the reasons set forth above, applicants maintain that the grounds for the Examiner's rejections have been overcome and respectfully request that the Examiner reconsider and withdraw these grounds of rejections and allow the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $1,050.00 fee for a petition for three-month extension of time, is deemed necessary in connection with the filing of this Amendment. If any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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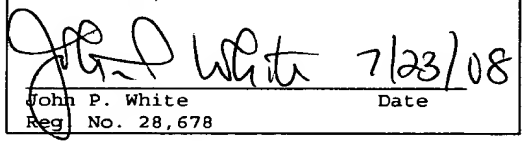

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EXHIBIT A